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Influence of postoperative pain and use of NSAID on heart rate variability of dairy cows

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Summary

This Research communication describes the effect of post-operative pain and NSAID treatment on heart rate variability (HRV) of dairy cows. Postoperative pain in farm animals is often left untreated. HRV could be a promising tool for pain assessment in animals. The aim of this study was to assess if postoperative state after subcutaneous surgery and NSAID treatment affect HRV in dairy cows. Nine cows were inserted with an implantable electrocardiograph logger. Cows were divided into the NSAID treatment group and the control group. The cows in the NSAID group had higher HRV than the control group, indicating a higher sympathetic activity in control animals, most likely due to untreated post-operative pain. Besides the ethical need for treating pain in production animals, ongoing pain has an adverse effect on animal productivity. Thus post-operative pain alleviation is recommended.

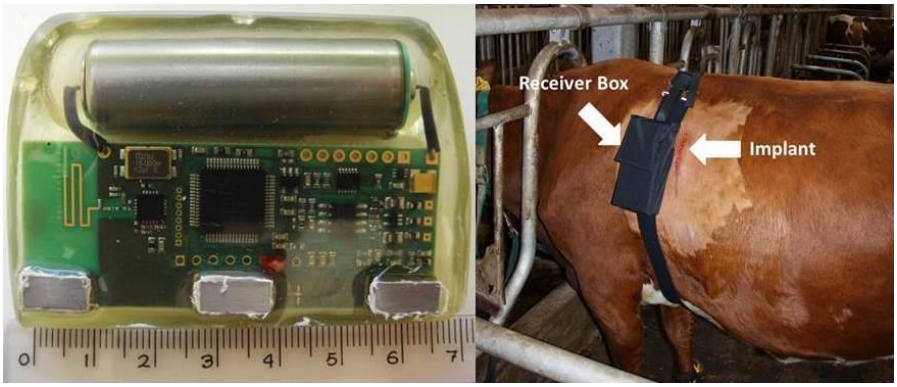
Key words: Dairy cattle, Heart rate variability, Pain, Nonsteroidal anti-inflammatory drug

In most cases involving farm animals, intraoperative pain during veterinary procedures is treated properly, but treatment for postoperative pain is seldom given (Walker *et al.* 2011). Behaviours, such as restlessness, foot stamping and changes in lying behaviour, are used for assessing farm animal pain, but also physiological parameters, such as stress hormones, are assessed (Viñuela-Fernández *et al.* 2007). However, both behavioural and traditional physiological approaches have their limitations in sensitivity and reliability and new methods for effective pain assessment are needed. Heart rate variability (HRV) can be used as an indicator of the sympathovagal balance of the autonomous nervous system (Task Force 1996) and HRV is a promising tool for pain assessment in farm animals (calves: Stewart *et al.* 2008 and 2010; ewes: Stubsjøen *et al.* 2009). However, results of HRV measurements are inconsistent: pain has been shown either to increase sympathetic (e.g. Stewart *et al.* 2008, Stubsjøen *et al.* 2009) or vagal (e.g. Stewart *et al.* 2010) activity. Thus there is a need for greater understanding of the underlying mechanism of HRV response, especially for different types of pain (e.g. somatic and visceral).

In cattle, studies on pain and HRV are mainly conducted with disbudded or castrated calves (Stewart *et al.* 2008, 2010) rather than with adult animals. The aim of the study was to assess if postoperative somatic pain after small-scale surgery and postoperative nonsteroidal anti-inflammatory drug (NSAID) treatment affect HRV in dairy cows. This experiment was a part of a larger study focusing on the effect of stress on HRV in dairy cows measured with implantable technology, and approved by the National Animal Experiment Board (Permit Number: ESHL-2008-08892/Ym-23).

Materials and methods

48 The study was conducted at the Natural Resources Institute Finland research barn in Maaninka,
49 Finland. The experimental animals were four pregnant heifers and seven dry cows (six Holstein-
50 Friesian and five Ayrshire). The animals were tethered in peat-bedded rubber-matted tie stalls
51 (width 120 cm, length 180 cm). They were fed daily with 0.3 kg of barley concentrate (energy
52 content 13.2 MJ ME/kgDM), 0.2 kg commercial mineral for dry cows (Tunnu-Namino, Hankkija Oy,
53 Finland), and 32 kg (multiparous cows) or 36 kg (heifers) grass silage (10.5 MJ ME/kgDM).
54
55 Implantable loggers (Bjarnason *et al.* 2013) were used to measure the electrocardiograph (ECG) of
56 the experimental animals (Fig. 1) with a sample rate of 341.3 Hz. The system contained a 50 g 70
57 mm x 45 mm x 17 mm) implant placed on the left side of the animal into a pocket made between
58 the skin and subcutaneous tissue posterior to the scapula, and a receiver box attached to the side
59 of the cow with an elastic girth.
60



61
62 Figure 1. a) Implant for ECG measurements and b) implant and receiver box after operating on the
63 cow.
64

65 The animals were operated about one month (± 3 days) prior to the expected parturition date
66 under sedation (0.018 mg/kg xylazine hydrochloride 20 mg/ml intravenously) and local anesthesia
67 (20 – 35 ml lidocaine hydrochloride 20 mg/ml subcutaneously). The animals received three-day
68 antibiotic treatment (20 000 IU/kg penicillin benzathine and penicillin procaine 300 000 IU/ml
69 intramuscularly) post-operatively.
70
71 Heifers and cows were randomly divided into the treatment (1 heifer + 5 cows) and the control (3
72 heifers + 2 cows) groups. On the operation day the treatment group received intravenous NSAID
73 treatment (3 mg/kg ketoprofen 100 mg/ml). An oral NSAID treatment (4 mg/kg ketoprofen 160
74 mg/g) mixed in a small amount of concentrates continued for the four consecutive days (days 1 –
75 4) after the operation day. The control group did not receive any NSAID treatment, but a small
76 amount of concentrates as a control treatment on the days 1 – 4. An oral ketoprofen has been
77 effectively used previously e.g. with acute mastitis in dairy cows (Banting *et al.* 2008).
78
79 ECG of the experimental animals was measured and behaviour video recorded during days 1 – 4
80 using cameras (Axis Q1755-E and Axis 215) positioned to face downwards to the tie-stalls. The
81 body and head postures and rumination of the animals were recorded continuously twice daily,
82 05.00 – 07.00 and 22.00 – 24.00. Because the posture of the animal affects the HRV (Frondelius *et*
83 *al.* 2015) only the ECG data from continuous lying periods (sternal recumbency while head up)
84 from animals not ruminating were used for the HRV analysis. ECG data from these periods were
85 visually inspected and good quality five-minute segments were selected for further analysis. Data
86 from two control group animals were discarded because of unreadable ECG data due to
87 malfunctioning of the implants.
88

The ECG data were interpolated to 500Hz using a geometric interpolation method (Tiusanen *et al.* 2015) and the location of the S wave (Tiusanen & Pastell 2016) was used to analyze the normal-to-normal (NN) intervals. We calculated heart rate (HR), the standard deviation of NN intervals (SDNN), root mean square of successive NN interval differences (RMSSD) and pNN50 (Task Force 1996).

HRV data from the nine animals (treatment n=6, control n=3) were used for the analysis including mean daily values of HRV parameters from 94 five-minute segments; 58 segments from the treatment group and 36 segments from the control group, 10.4±5.87 (mean±SD) segments per cow. Linear mixed models were fitted to determine the effect of independent variables – treatment (control vs NSAID), time from the procedure (days 1 – 4) and the interaction between these two – on HRV parameters (dependent variables) using compound symmetry as a covariance structure and cow as a random effect. The statistical analyses were made with SAS for Windows version 9.2 through SAS Enterprise Guide version 4.3 (SAS Institute Inc., Cary, NC, USA).

Results and discussion

The cows in the treatment group had higher SDNN and tended to have higher RMSSD values than the animals in the placebo group (Table 1). There were no differences in HR and pNN50 between two groups. The day did not have any effect on HRV values and there was no interaction between the treatment and the day.

Commented [FL1]: *Table 1 near here*

The results indicate that NSAID affects the postoperative HRV of adult dairy cows that had undergone subcutaneous implantation. The control group had a lower vagal tone and a stronger sympathetically controlled response (von Borell *et al.* 2007) to the postoperative state, most likely

113 due to untreated pain. Ketoprofen might have also mitigated the inflammatory reaction towards
114 the implant due to NSAIDs anti-inflammatory and anti-pyretic effects (Donalisio *et al.* 2012).
115
116 We did not observe any effect of NSAID treatment on long-term HR. This result is similar to
117 Raekallio et al (1997), who studied horses for 72 hours after arthroscopic surgery. Generally higher
118 sympathetic activity is connected to increase in HR (Von Borell *et al.* 2007) and lack of pain
119 medication increases HR (Stewart *et al.* 2008, Stubsjøen *et al.* 2009). In these studies, however, HR
120 was measured only during the painful procedure or few hours after it. This difference in methods
121 may partly explain lack of difference in HR in our study, since we started measurements of cardiac
122 responses one day after the surgery and measured it throughout the whole four-day post-
123 operative treatment. However, it is also possible that ketoprofen was not a potent enough NSAID
124 to cause differences in HR, as in the study by Newby *et al.* (2014).
125
126 With this small number of the animals, our experiment should be regarded as a case study.
127 However, linked with other results, we suggest that HRV may be a sensitive measure for assessing
128 pain in production animals. Stubsjøen *et al.* (2009), who also used a limited number of animals in
129 their study, found that moderate pain in sheep had an effect on HRV.
130
131 This study shows that dairy cows are subjected to postoperative pain even after small-scale
132 subcutaneous surgery. In production animals postoperative pain is often neglected (Walker *et al.*
133 2011). Besides the ethical need for treating pain, ongoing pain may also have an adverse effect on
134 animal productivity, affecting their growth and immune functions (Anil *et al.* 2005). Thus pain
135 alleviation during and after painful procedures is beneficial for the animal, the producer and the
136 consumer.

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Table 1. Comparison of the linear mixed model estimates of heart rate variability (HRV) variables (mean±SEM) between NSAID (cows n=6; analyzed 5-minute HRV segments n=58) and placebo groups (cows n=3; analyzed 5-minute HRV segments n=36).

	NSAID	Placebo	P
HR	61.0±3.84	61.8±5.55	ns

SDNN	56.1±2.16	45.6±3.39	<0.05
RMSSD	60.8±1.96	54.3±3.09	<0.1
pNN50	6.21±1.58	4.96±2.40	ns

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